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PRINCIPAL INVESTIGATOR: Garrett A. Smith, M.D.
I. Craig Henderson, M.D.

CONTRACTING ORGANIZATION: University of California, San Francisco
San Francisco, California 94143-0962

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Garrett A. Smith, M.D.
I. Craig Henderson, M.D.

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San Francisco, California 94143-0962

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13. ABSTRACT

This project continues to develop and refine a novel clinical curriculum that utilizes resources from diverse disciplines. I have combined sub-specialty training in oncology with formal courses in biostatistics, epidemiology, and health policy research, in order to develop expertise in clinical trials methodology and health care reform. The Clinical Research Scholars Program served as a foundation in outcomes research during the first year of the project, the second year of the project focused on an in depth analysis of high-dose chemotherapy with peripheral blood stem cell transplant as a treatment for breast cancer. Specifically, outcomes research methodology highlighted a comprehensive review of HDC for breast cancer, and compared this technology to other new treatments for breast cancer. Technology assessment serves a vital role the design of clinical pathways in an expanding managed care marketplace. Specific evidence-based guidelines were generated in an attempt to clarify the controversy surrounding the investigational nature of HDC, and explore the impact of this new technology on practice patterns and 3rd-party payers coverage. During the final phase of the training grant, a new outpatient high-dose chemotherapy program will be implemented at the University of California, San Francisco with particular emphasis on quality-of life and cost-benefit analysis. The goal is to incorporate outcomes assessment into a Managed Care marketplace.

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Carol C Lind 8/28/91

PI - Signature Date

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INTRODUCTION

Background

Last year 182, 000 women in the United States were diagnosed with breast cancer. Experts agree that median survival has not changed appreciably in the past 5 decades, and it is estimated that over 45,000 women will die each year from metastatic disease. Because so many women are affected, breast cancer research receives the largest allocation of federal funding in this country. In 1993, over 260 million federal research dollars will be invested in breast cancer research. This funding does not include the enormous resources spent each year by Third-party insurers for the screening, diagnosis and treatment of women with breast cancer in the United States.

High-dose chemotherapy with autologous bone marrow transplantation (HDC/ABMT) technology has advanced dramatically over the past decade. Enthusiasm for this method of treatment has flourished, despite the absence of any prospective randomized data to compare this investigational treatment with conventional chemotherapy for advanced disease. A variety of studies clearly document higher complete response rates and overall response rates in patients treated with HDC/ABMT. However, these patients have similar survival duration, and the duration of response is no different when HDC patients are compared to patients treated with conventional therapy. Thus, the lack of controlled clinical trials has resulted in data which are extremely difficult to interpret and public expectations which are currently unfounded. Nevertheless, public expectation of this treatment far exceeds the reality of published results.

HDC/ABMT has generated an intense health policy debate, because the financial cost of such treatment is enormous. Third-party insurers still consider this treatment investigational, and frequently deny coverage for the $60,000-$100,000 estimated cost for each transplant. As a result, many patients are now suing insurance carriers who don't cover this therapy. The Managed Care environment has also forced hospitals to reconsider widespread application of a once profitable treatment, as they have been forced to negotiate for HDC/ABMT contracts, often at or below cost.

As a consequence of uncontrolled trials, data exists that allows an investigator to support a variety of conclusions. This dilemma is highlighted by two large literature reviews that

appeared almost simultaneously in 1992 oncology journals, but came to opposite conclusions. K. Antman, a pioneer in the development of high-dose chemotherapy regimens used with autologous bone marrow transplant, reviewed all trials in which women with advanced breast cancer who were treated with bone marrow transplantation. In this article, "Progress in Chemotherapy for Metastatic Breast Cancer" (*Seminars in Oncology* 19: 317-332, 1992), three sets of uncontrolled studies were viewed favorably based on a comparison of complete response rates to historical controls. The authors conclude that, "un-maintained responses appear to be encouraging in patients who are transplanted early in the course of their disease, and after a good response to standard dose chemotherapy."

David Eddy of the Center for Health Policy Research and Education at Duke University, and advisor to the Blue Cross / Blue Shield National Association Technology Assessment Panel reaches an entirely different conclusions from the same clinical trials data. His review, "High-Dose Chemotherapy with Autologous Bone Marrow Transplantation for the Treatment of Metastatic Breast Cancer" (*Journal of Clinical Oncology* 10: 657-670, 1992), explains that "firm conclusions are not possible because of the lack of controlled studies, and the presence of numerous biases.

I. Craig Henderson also asserts that current breast cancer trials in women with advanced disease are "sufficiently promising to justify comparative trials, but insufficient to conclude that the therapy is superior to more conventional treatments." In his editorial, "Window of Opportunity." he further outlines the scope of the debate involving the high costs of bone marrow transplant in terms of toxicity and the shrinking resources available to fund large clinical trials.(*Journal of the National Cancer Institute* 83: 894-896, 1991) Henderson reports that the National Blue Cross / Blue Shield Association recently created a fund the help the National Cancer Institute sponsor clinical trials. Such collaboration between third-party payers and clinical investigators is imperative in the current setting of health care reform , in order to cover the "costs of legitimate research approved by peer review groups outside the investigator's own institution."

The controversy surrounding high-dose chemotherapy as a treatment for breast cancer has recently intensified with the first publication of a randomized trail supporting concept of dose-intensity. (*Journal of Clinical Oncology* 13(10):2483-2489, 1995) High dose chemotherapy (HD-CNV) was administered as a two step tandem regimen at doses of 2.4 g/m^2 cyclophosphamide, 35-45 mg/m^2 of mitoxantrone, and 2.5 g/m^2 of etoposide. The control arm used 6-8 cycles of a conventional dose schedule (CNVr) with 600 mg/m^2 of

cyclophosphamide, 12 mg/m^2 of mitoxantrone, and 1.4 mg/m^2 of vincristine. The response rates were significantly higher in the high-dose patients (95% vs 53%) with 51% of the high-dose patients achieving a complete response. Disease-free survival was prolonged with HD-CNV (80 weeks vs. 34 weeks) and overall survival was twice that of the standard dose regimen (90 weeks vs. 45 weeks). The statistical significance of these survival differences was not reported. Although not definitive, this positive study will be championed by advocates of dose intensity, and health policy decisions regarding patients selection, specific drug regimen, and insurance reimbursement now have an urgent priority.

Proposal Outline

This proposal creates a novel curriculum in clinical outcomes research that utilizes multiple resources from diverse disciplines.

A.G. Mulley, a pioneer in the field of outcomes research, stresses the increasing problems associated with cost and access to health care. In a draft manuscript, "Outcomes Research: Potential, Prospects & Policy Implications," he defines outcomes research as the "generation, collection, and analysis of information about the results or outcomes of medical care for the purpose of learning how to improve those results. He outlines 4 specific types of research that directly applies to the debate about bone marrow transplantation in advanced breast cancer:(Outcomes Research: Potential, Prospects and Policy Implications. 1993)

1) Studies that observe variation in the process of medical care.
2) Studies that observe variations in the outcomes of care.
3) The development of instruments to measure outcomes of care.
4) The study of patient preferences.

Eddy also addresses the issues of patient outcomes in his review, when he describes the 5%-15% treatment related mortality involved in bone marrow transplantation, as well as the complication rate of 30%. He also defines outcomes that have not yet been specifically analyzed in current clinical trials, to the detriment of drawing legitimate conclusions.

1) Overall survival
2) Relief of symptoms
3) Risk of treatment
4) Side effects of treatment

Eddy finally concludes that response rates are not sufficient outcomes, and thus, can not be sole basis for treatment decisions. Instead researchers must define how patient outcomes can and should affect medical decision making. Outcomes research methodology will provided useful tools for the analysis of the transplant controversy. Specific questions to be addressed remain, which have critical importance in resource allocation and health care reform:

1) Do women live longer with a bone marrow transplant
2) Do women spend a significantly greater period of time without side effects of therapy or symptoms of disease than they would with conventional therapy?
3) What do women understand are the benefits of transplant?
4) What are physician expectations for this therapy?
5) Do the benefits of treatment justify the costs?

Thus, high-dose chemotherapy with autologous bone marrow transplant represents an enormous public health issue, and this clinical fellowship proposal has been developed to prepare a clinical oncologist for the academic arena of health services research and health care reform. Sub-specialty training in medical oncology will be combined with formal courses in biostatistics, health services research and technology assessment, in order to develop expertise in clinical trials methodology and health policy issues.

Preliminary work based on this training will involve the development of specific outcome models and instruments to assess individual patient preferences and satisfaction with various treatment options. Such tools will be invaluable in an analysis of the quality of medical care received by women with breast cancer in the United States. Moreover, they are important measurements of the impact that existing physician practice has on the quality and cost of health care. The expanding presence of Managed Care in California has made outcomes research a vital priority, as evidence-based medicine will soon dictate breast cancer practice patterns and insurance coverage.

BODY OF REPORT

YEAR 1

I successfully completed both objectives for the first year of the project.

Develop an in-depth understanding of the natural history and medical management of breast cancer.

The essential core of this curriculum involves in-depth specialty training in the treatment of breast cancer patients. I have completed the clinical fellowship in medical oncology at the University of California, San Francisco, and focus on the outpatient care of women with breast cancer at the UCSF / Mount Zion Breast Cancer Clinic. This multi-disciplinary clinic provides a unique opportunity to focus on a select group of patients under the guidance of Drs. I. Craig Henderson, Chris Benz, Charles Dohlbaum and Debu Tripathy from the division of Medical Oncology, Drs. Laura Esserman and William Goodson from the Department of Surgery, and Dr. Laurence Margolis from the department of Radiation Oncology. Drs. Henderson, Tripathy, Esserman and Margolis have primary offices in the Breast Clinic, and will provide daily instruction. All of these physicians are breast cancer specialists, who serve as vital resources during weekly clinics and conferences. I will continue to participate in this weekly clinic and multi-disciplinary conference for the remainder of my fellowship training project.

As a result of my participation in the breast cancer multi-disciplinary clinic, I have developed two Phase II/III clinical trials involving Vinorelbine as a treatment for metastatic breast cancer. These studies will incorporate significant quality-of-life and resource utilization outcomes that are a direct result of this project. Both trials have just been accepted by the Human Subjects Committee, and are open for patient accrual.

I have also expanded my role in the clinic to include primary teaching responsibilities. I directly supervise fellows in our Division, and have precepted numerous medical students and residents. I particularly emphasize cost-

effectiveness, managed care and quality of life issues in the care of patients with breast cancer.

Master the methodology of clinical trial design

During the first year of this research fellowship, I completed the Clinical Research Scholars Program at U.C.S.F. This combined program in the departments of Medicine, Epidemiology, and Biostatistics consisted of a 1-year core curriculum in clinical research, with a specific goal to "train the scholar to conceive, plan, and conduct state of the art clinical research, and analyze the results of research appropriately." The Clinical Scholars Program included comprehensive training in statistical methods and data analysis, as well as the specifics of clinical trial design. Particularly relevant topics included decision analysis, cost-effectiveness research, and computer-based data management. During the monthly "Work in Progress Seminar," I designed a Phase II trial involving Vinorelbine and Paclitaxel as a combination treatment for metastatic breast cancer. This trial has been approved by the Human Subjects Committee, and will be open to patient accrual in September.

The second half of the course involved in depth health care policy and outcomes research, and was taught by faculty from both the Department of Epidemiology and the Institute for Health Policy Studies. These 3 hour/week didactic sessions have provided an excellent foundation for future independent study, particularly cost-benefit analysis and managed care issues in health policy.

YEAR 2

Based on the foundation provided by the breast clinic and the Clinical Scholars Program, I completed two key objectives during the second year of the project:

Learn the fundamentals of patient outcomes research, medical economics, and health care policy, in order to critique a new technology.

This fellowship proposal involves patient outcomes research training, and the application of specific tools to examine patient outcomes in the development and implementation of high-dose chemotherapy (HDC/ABMT) for breast cancer.

A) Critical literature reviews

During the second phase of my training, I published a comprehensive review of high-dose chemotherapy with autologous bone marrow transplant for women with breast cancer, which emphasized the health policy debate surrounding this controversial treatment (Smith, GA, Henderson, IC, "High-dose Chemotherapy with Autologous Bone Marrow Transplantation for the Treatment of Breast Cancer: The Jury Is Still Out," *Important Advances in Oncology 1995*, DeVita, V.T. ed, 1995, pp. 201-214.). This article provided an opportunity to review the available literature, and critically examine the issues surrounding an investigational therapy.

I have also completed a manuscript which examines the role of Phase I/II investigational therapies in the breast cancer armamentarium. (Smith, GA, Henderson, IC, "New Treatments for Breast Cancer," Seminars in Oncology 23(4) pp. 506-528.) In this review, I included the results from the first published randomized controlled trial which involved HDC/ABMT as a treatment for advanced breast cancer. Until more supportive data are available. HDC is not an established standard therapy and remains investigational at this time.

In collaboration with Dr. Henderson, I have completed a manuscript draft entitled "Management of Metastatic Breast Cancer," which provides a detailed review of chemotherapy treatment options for women with breast cancer. I specifically critique HDC in detail, and examine the impact of patient selection, small numbers of patients, and brief follow up, which introduces substantial bias and must temper the

preliminary results reported to date. I also emphasize outcomes research methodology in an attempt to define treatments guidelines from an evidence-based medicine approach. My major emphasis will be the study of patient preferences, physician decision-making, quality of life issues associated with high-dose chemotherapy and peripheral blood stem cell support as a treatment for breast cancer. Specifically, I will utilized cost-effectiveness and decision analysis methodology to create a detailed algorithms in order to identify the optimal treatment for specific groups of women with advanced breast cancer and patients who would be appropriate candidates for high-dose adjuvant therapy. I expect this model to appear in peer-reviewed literature, and to serve as a tool for managed care and insurance company reimbursement decisions.

B) Blue Cross/Blue Shield Technology Assessment

I had originally intended to base the technology assessment component of this project at the Institute for Health Policy and the National Blue Cross/ Blue Shield Association. Instead I was given the opportunity to work directly with the Michigan Blue Cross /Blue Shield on a specific HDC/ABMT project.

Despite specific exclusions for "investigational or experimental therapies" in their health plan, BCBS has been forced to provide coverage for HDC as a treatment for breast cancer, despite the absence of conclusive data to support is use as a standard therapy. In preparation for extensive class action litigation, BCBS of Michigan solicited a comprehensive assessment of HDC/PBSC for breast cancer. I completed an exhaustive review of the medical literature for Medical Director Seymore Adelson M.D., and provided a detailed annotated bibliography to serve as a permanent resource for BCBS, and as a general reference for their legal counsel.

I also critically interpreted al of the available evidence, and prepared a technology assessment overview of HDC/ABMT for metastatic and high-risk primary breast cancer. I incorporated cost-effectiveness and decision analysis information that has become available, and determined that at the present time (5/96) that high-dose chemotherapy with peripheral blood stem cell transplantation remain investigational.

This project remains active, and I anticipate a future role as an advisor to the Michigan group as they deal with the evolving HDC/ABMT technology, and pending

litigation. I expect to participate in the process of implementing new policies for coverage for their members.

YEAR 3

The ultimate goal of my proposal will be to apply the diverse outcomes research training background to develop specific breast cancer research projects.

Apply outcomes research models to specific projects for high dose chemotherapy as a treatment for breast cancer.

A) UCSF Pilot outpatient ABMT program

Instead, I have broadened the scope of my specific outcomes projects to include a specific project at the University of California, San Francisco. Dr. Lee Goldman, Chairman of the Department of Medicine has agreed to serve as a mentor for this breast cancer project related to heath care outcomes of particular importance in a Managed Care environment.

I have joined the clinical bone marrow transplant team, and perform high-dose chemotherapy with peripheral blood stem cell transplant for women with breast cancer. We are participants in the national CALGB randomized trial comparing HDC to standard therapy for women with > 10 point axillary lymph nodes. We also have a phase II protocol utilizing HDC for patients with either metastatic breast cancer patients and women with high-risk primary breast cancer. As an attending physician, I directly supervise the medical housestaff and have direct patient contact on a daily basis. The transplant team has weekly multi-disciplinary rounds where the emphasis is placed on quality-of-life outcomes, as well as the opportunity to plan clinical trial design.

In collaboration with transplant director Dr. Charles Linker, and senior faculty members Drs. Curt Reis and Lloyd Damon, and Hope Rugo, I plan to develop an outpatient-based high-dose therapy protocol which will emphasize the importance of cost-effectiveness and quality-of-life. The entire treatment plan will prioritize

patients outcomes, and will be structured in such a fashion that additional research can be readily obtained.

Critical questions at this phase of the project include :

1) What outcomes are feasible to measure?
2) Can these outcomes be accurately and reliably measured?
3) Are the measurable outcomes important to patients?
4) Which outcomes are most important to a managed care plan?
5) What resources are required for HDC/ABMT?
6) Can a cost-benefit analysis identify a superior treatment?

An outpatient program of high-dose chemotherapy with bone marrow transplantation provides an excellent model for the study of patient outcomes research. Until recently, the lack of controlled clinical trials generated intense debate within the medical profession about the effectiveness of this treatment,, and a tremendous enthusiasm in the community for an unproven treatment. Now that randomized trials are providing supportive evidence in certain patients, the need for proper outcomes-based protocol design is imperative, particularly in the Managed Care driven market of Northern California.

B) MediCal Patient Outcomes

In the state of California, MediCal does not cover HDC as a treatment for breast cancer. At our institution we have a referral network and informational database which can identify women with breast cancer that were denied access to HDC based on their Medical insurance coverage.

I hope to collaborate with Dr. Hope Rugo on a project that will compare the long-term outcomes of Medical patients treated with standard therapy to similar women referred to UCSF for HDC protocols for both advanced disease and high-risk women with > 10 positive axillary lymph nodes. As a preliminary step, I will examine the cost and survival data on our HDC patients at UCSF. This information is readily available in our database. I will then attempt to locate all Medical patients referred to UCSF by our Northern California community physicians. These MediCal patients were not treated with HDC, and I will investigate their survival and cost data. A comparison of MediCal patients to our HDC protocol patients should provide

valuable information concerning the impact of insurance coverage (an indirectly socioeconomic status) on patient survival, quality-of-life, and treatment cost.

C) Lange Current Medical Diagnosis and Treatment

I am the principle editor for a new oncology edition of the Lange series textbook scheduled for publication in 1997. I will emphasize HDC/ABMT, technology assessment and outcomes research in a special chapter entitled "Managed Care Oncology." I believe that the ultimate adoption of HDC technology can only be based on a comprehensive analysis of cost-effectiveness, quality-of-life, and overall survival. The driving force will likely be health care administrators, not research physicians.

This material will serve as an excellent example of the goals of entire project, and I plan to present the information at the Breast Cancer Research Program in the Spring of 1997.

D) Managed Care at UCSF

As a result of this training grant, I have embarked on a clinical pathway at the University of California, San Francisco. The health care arena has prompted academic centers to change dramatically to face new economic realities (Wachter, R.M., Goldman, L., "The Emerging Role of 'Hospitalists" in the American health Care System," *New England Journal of Medicine*, 335(7) pp. 514-517.) I am a assistant clinical professor on the inpatient medical service, where I directly supervise and teach a group of students and residents. I particularly emphasize outcomes research techniques such as decision analysis, cost-effectiveness, and evidence-based medicine. The technology assessment example provided by HDC/ABMT serves as a valuable template for housestaff training.

I am also involved in a plan to redefine the role of a community oncologist. After the project is completed, I hope to acquire a private oncology practice, and transform it into an academic, managed care oncology service which can care for patients and produce quality outcomes research projects at UCSF.

CONCLUSIONS

This annual report documents the successful completion of the first 2 years of a three year novel clinical education in outcomes research. I have completed sub-specialty training in breast cancer through participation in a unique, multi-disciplinary clinic at the University of California, San Francisco. This training has resulted in several independent Phase II/III trials of new treatments for breast cancer, which emphasize importance of quality of life and resource utilization outcomes as primary reassert endpoints. I have also completed the Clinical Research Scholars Program, which has provided an excellent foundation for heath care outcomes research.

In second year of the project, I focused on high-dose chemotherapy with bone marrow transplant (HDC/ABMT) as a model for technology assessment. I have 3 breast cancer publications based on this research, which critically examine the evidence supporting HDC/ABMT as a treatment for breast cancer. I continue to serve as a medical advisor for the Michigan Blue Cross/Blue Shield, and have reviewed HDC/ABMT for their legal counsel, and generated recommendations supporting the investigational nature of HDC at this time.

I have also initiated plans to develop a managed care analysis of HDC/ABMT at UCSF, and will assist in the development of an outpatient HDC treatment protocol at our institution, which will serve as a model for subsequent outcomes analysis.